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STOCHASTIC FORMULATION OF A REPAIR-FIXATION MODEL FOR DNA DAMAGE FROM IRRADIATION

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Abstract

Stochastic formulation of a repair-fixation model for DNA damage from irradiation was studied. The model may be used to predict the distribution of mutations and the probability of cell survival.

Keywords: repair-fixacion model.

Irradiation experiments (ELKIND and WHITMORE, 1982, METTING et al, 1985) have led to the observation that cell lesions arising from irradiation may be repaired or are converted to mutations (fixed). We consider first that the number of lesions (i) induced by exposure to radiation of a given dose follows a given probability distribution, $P(i)$. Based on data from different irradiation experiments (VIRSIK and HARDER, 1981), $P(i)$ may be assumed to be Poisson or Poisson–Poisson (clustered). Cells carrying initial lesions are said to be in state S. A lesion in state S may at any time be repaired and transformed into state R or be fixed and transformed into state F.

Let $P_{i-k}(t)$ = probability of observing $(i-k)$ lesions in state S at time t; $(k = 0, 1, 2, \ldots, i)$.

It can be shown that

$$P_{i-k}(t) = (-1)^k \mu_i \mu_{i-1} \ldots \mu_{i-k+1} \left[\frac{\sum_{j=0}^{k} e^{-\mu_{i-j} t}}{\prod_{\substack{l=0 \\ l \neq j}}^{k} (\mu_{i-j} - \mu_{i-l})} \right], \qquad (1)$$

$$(k = 1, 2, \ldots, i-1),$$

$$P_i(t) = e^{-\mu_i t} \qquad (2)$$

and

$$P_0(t) = (-1)^{i-1}\mu_i\mu_{i-1}\dots\mu_2\mu_1\left[\frac{\sum_{j=0}^{i-1}\left(e^{-\mu_{i-j}t}-1\right)}{-\mu_{i-j}\prod_{\substack{l=0\\ l\neq j}}^{i-1}(\mu_{i-j}-\mu_{i-l})}\right]. \qquad (3)$$

Here, $\mu_i = \alpha_i + \beta_i$ where
α_i = the intensity of transition from state S to state R and
β_i = the intensity of transition from state S to state F.

The transition intensities α_i and β_i can be chosen in general to be any function of the number lesions i in state S.

Given i lesions initially, it is seen that the probability that n lesions are fixed at time t, $q_{n|i}(t)$ is

$$q_{n|i}(t) = \sum_{k=0}^{i} P_{i-k}(t)P_r[n|k]\,; \qquad (n = 0, 1, 2, \dots, k). \qquad (4)$$

The unconditional probability is

$$q_n(t) = \sum_{i=1}^{\infty} q_{n|i}(t)p(i) + p(0)\,. \qquad (5)$$

In *Eq.* (4), $P_r[n|k]$ is the probability that from k outcomes, n are in state F and $k-n$ in state R. This is obtained from the intensities α_i and β_i, adding the probabilities of all possible combinations of n F's and $(k-n)$ R's.

It is seen that when the probabilities of fixation $(1-p)$ and repair (p) are independent of $(i-k)$,

$$P_r[n|k] \quad \text{is binomial} \quad = \binom{k}{n}p^n(1-p)^{k-n}.$$

Given i initial lesions $(i \geq 1)$, the probability of cell survival at time t, $PS_i(t)$, can be obtained in general from the distribution of mutations in *Eq.* (4) under different assumptions. Here we shall assume that a fixed lesion has a certain probability φ of surviving. As such, one has

$$PS_i(t) = \sum_{k=0}^{i}\sum_{n=0}^{k} P_{i-k}(t)P_r[n|k]\Phi^n\,. \qquad (6)$$

The unconditional probability of survival

$$PS(t) = \sum_{i=1}^{\infty} PS_i(t)p(i) + p(0). \tag{7}$$

The probability of survival in *Eq.* (7) is developed based on the assumption that repair and fixation in the case of a Poisson–Poisson distribution or clustering is global and not localized within a cluster. Repair and fixation may be locally mediated through enzymes whose kinetics follow the Michaelis–Menton equation (KIEFER, 1988). For this case, the probability of survival was derived assuming that repair and fixation occur locally within each cluster with independence among clusters.

Model equations may be fitted to experimental data to estimate parameters and to aid in design of experiments and interpretation of results. Also, the model may be used to predict the distribution of mutations and probability of cell survival.

References

ELKIND, M. M. – WHITMORE, G. F. (1982): The Radiobiology of Cultured Mammalian Cells. Gordon and Breach, New York.

KIEFER, J. (1988): A Repair-fixation Model Based on Classical Enzyme Kinetics. Quantitative Mathematical Models in Radiation Biology. Springer, Berlin, New York, pp. 171–179.

METTING, N. F. – BRABAY, L. A. – ROESCH, W. C. – NELSON, J. M. (1985): Dose-rate Evidence for Two Kinds of Radiation Damage in Stationary-phase Mammalian Cells. *Radiat. Res.*, Vol. 103, pp. 204–218.

VIRSIK, R. P. – HARDER, D. (1981): Statistical Interpretation of the Overdispersed Distribution of Radiation Induced Dicentric Chromosome Aberrations at High LET. *Radiat. Res.*, Vol. 85, pp. 13–23.